(12) UK Patent Application (19) GB (11) 2 150 932 A

(43) Application published 10 Jul 1985

(21) Application No 8430810

(22) Date of filing 6 Dec 1984

(30) Priority data

(31) 8332435 (32) 6 Dec 1983 (33) GB

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(51) INT CL⁴
C07D 209/14 A61K 31/40

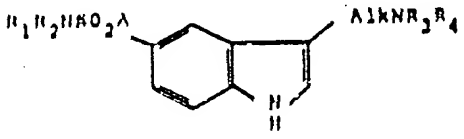
(52) Domestic classification
C2C 1343 1344 200 213 220 226 227 22Y 246 247 250 251 25Y 28X 29X 29Y 304 305 30Y 321 322 323 326 327 328 32Y 332 342 34Y 351 352 355 360 361 366 367 36Y 385 395 39Y 510 512 51X 51Y 532 533 534 536 537 538 60Y 620 650 652 660 680 699 800 802 80Y AA RJ SJ U1S 2415 C2C

(56) Documents cited
None

(58) Field of search
C2C

(54) Indoles

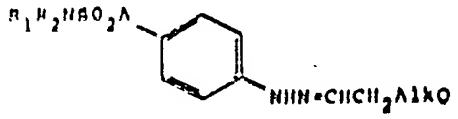
(57) Indole derivatives are disclosed of the general formula (I):



(I)

(wherein R_1 is hydrogen, C_{1-6} alkyl or C_{3-6} alkenyl; R_2 is hydrogen, C_{1-3} alkyl, C_{3-6} alkenyl, phenyl, phen(C_{1-4})alkyl or C_{5-7} cycloalkyl; R_3 and R_4 are hydrogen, C_{1-3} alkyl or propenyl or together form an aralkylidene group; Alk is a C_2-C_4 alkylene chain and A is a C_2-C_5 alkylene chain) and their physiologically acceptable salts and solvates.

The compounds may be prepared by cyclisation of a compound of general formula (II):



(II)

where Q is the group NR_3R_4, a protected derivative thereof or a leaving group.

The compounds have a selective vasoconstrictor action and are useful in treating pain such as migraine.

SPECIFICATION

Chemical compounds

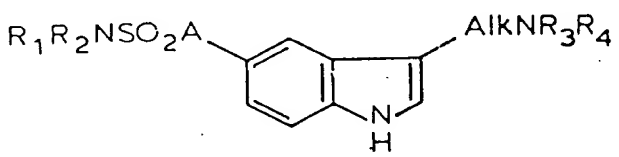
This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

The pain of migraine is recognized as being primarily of vascular origin, caused by excessive dilatation of the cranial vasculature. Known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic usually in combination with an antiemetic but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

We have now found a group of indole derivatives having potent and selective vasoconstrictor activity.

The present invention provides an indole of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group;

R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl, phenyl, phen(C_{1-4})alkyl or C_{5-7} cycloalkyl group;

R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl or 2-propenyl group or R_3 and R_4 together form an aralkylidene group;

Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups; and

A represents an alkylene chain containing two to five carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups, and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The invention includes within its scope all optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof.

Referring to the general formula (I), the alkyl groups in the general formula (I) may be straight chain or branched chain alkyl groups containing 1 to 3 carbon atoms, or, in the case of R_1, 1 to 6, preferably 1 to 3, carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl and isopropyl groups. The alkenyl groups preferably contain 3 or 4 carbon atoms, examples being propenyl and butenyl groups. It will be understood that when R_1 or R_2 is an alkenyl group the double bond must be separated from the nitrogen atom by at least one methylene group. The cycloalkyl groups preferably contain 5 or 6 carbon atoms and examples include cyclopentyl and cyclohexyl groups. The alkyl moieties of the phenalkyl groups preferably contain 1 or 2 carbon atoms as in e.g. benzyl and phenethyl groups. The aralkylidene group is preferably an aryl methylidene group such as benzylidene.

In the compounds of general formula (I) it is preferred that at least one of R_1 and R_2 represents hydrogen.

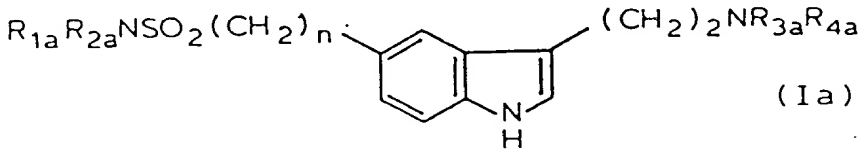
A is preferably an unsubstituted alkylene chain containing two to five carbon atoms, especially two or three carbon atoms. Alk is preferably an unsubstituted alkylene chain, especially an unsubstituted alkylene chain containing two carbon atoms.

A preferred class of compounds represented by the general formula (I) is that in which R_1 represents a hydrogen atom or a C_{1-6} alkyl group and R_2 represents a hydrogen atom or a C_{1-3} alkyl, or phen(C_{1-4}) alkyl group.

Another preferred class of compounds represented by the general formula (I) is that in which A represents the $-CH_2CH_2-$ group.

A further preferred class of compounds is that wherein, in the general formula (I), R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

A preferred class of compounds falling within the scope of general formula (I) is that represented by the general formula (Ia):



(Ia)

wherein

R_{1a} represents a hydrogen atom or a C_{1-3} alkyl group;

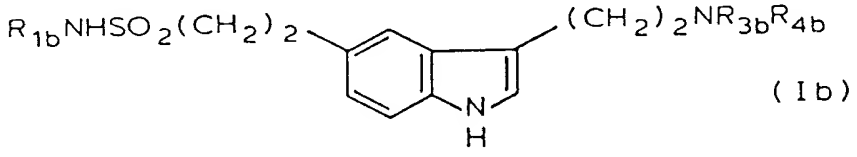
R_{2a} represents a hydrogen atom or a C_{1-3} alkyl, or phen(C_{1-2}) alkyl group;

R_{3a} and R_{4a} which may be the same or different each represents a hydrogen atom or a methyl or ethyl group; and

n represents 2 or 3,

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

A particularly preferred class of compounds according to the invention is that represented by the general formula (Ib):



(Ib)

wherein

R_{1b} represents a hydrogen atom or a C_{1-3} alkyl group; and R_{3b} and R_{4b}, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group;

and physiologically acceptable salts and solvates, (e.g. hydrates) thereof.

In compounds of formula (Ib) it is preferred that the total number of carbon atoms in R_{3b} and R_{4b} does not exceed two, and most preferably R_{3b} and R_{4b} each represents a methyl group.

Preferred compounds according to the invention include;

3-[2-(ethylamino)ethyl]-N-methyl]-1*H*-indole-5-ethanesulphonamide;

N-methyl-3-[2-(methylamino)ethyl]-1*H*-indole-5-ethanesulphonamide;

3-(2-aminoethyl)-N-methyl-1*H*-indole-5-ethanesulphonamide;

3-[2-(dimethylamino)ethyl]-1*H*-indole-5-ethanesulphonamide;

3-[2-(dimethylamino)ethyl]-N-methyl-1*H*-indole-5-ethanesulphonamide;

and the physiologically acceptable salts and solvates (e.g. hydrates) of these compounds.

Suitable physiologically acceptable salts of the indole of general formula (I) includes acid addition salts formed with organic or inorganic acids for example hydrochlorides, hydrobromides, sulphates, fumarates, maleates and succinates. Other salts may be useful in the preparation of the compounds of general formula (I) e.g. creatinine sulphate adducts and oxalates.

It will be appreciated that the invention extends to other physiologically acceptable equivalents of the compounds according to the invention, i.e. physiologically acceptable compounds which are converted *in vivo* into the parent compound. Examples of such equivalents include physiologically acceptable labile N-acyl derivatives such as the N-acetyl derivative.

Compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog, whilst having a negligible effect on blood pressure. The selective vasoconstrictor action of compounds of the invention has been demonstrated *in vitro*.

Compounds of the invention are useful in treating pain resulting from dilatation of the cranial vasculature, in particular migraine and cluster headache.

In particular, the compounds of formula (Ib) previously defined have been found to be highly selective vasoconstrictors and to be extremely potent in their action. Compounds of general formula I(b) are rapidly absorbed from the gastro-intestinal tract and are suitable for oral or rectal administration. Compounds of formula (Ib) exhibit no toxic or undesirable effects in rats at doses up to 6 mg/kg. At doses at which the compounds of formula (Ib) would be efficaceous in the treatment of migraine, the compounds have no significant effect on blood pressure and heart rate and no significant bronchoconstrictor effect on the lung.

Accordingly the invention also provides a pharmaceutical composition adapted for use in medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and which is formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Formulations of the compounds according to the invention for oral administration are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinyl-pyrrolidone or hydroxypropyl methylcellulose; fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch, sodium starch glycollate or croscarmellose); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives e.g. hydroxypropylmethyl-cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl *p*-hydroxybenzoates or sorbic acid). The liquid preparations may also contain conventional buffers, flavouring, colouring and sweetening agents as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parental administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents and/or agents to adjust the tonicity of the solution. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatine for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, rectal or buccal administration to man (of average body weight e.g. about 70 kg) for the treatment of migraine is 0.1 to 100 mg of the active ingredient per unit dose which could be administered, for example 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

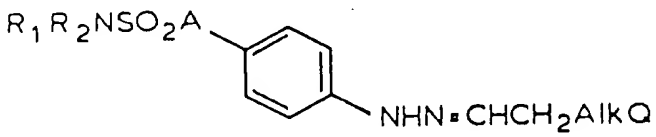
For oral administration a unit dose will preferably contain from 2 to 50 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 5 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or "puff" delivered from a pressurized aerosol contains 0.2 mg to 2 mg of a compound of the invention, and each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation will be within the range 1 mg to 100 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants.

According to another aspect of the invention, compounds of general formula (I) and their physiologically acceptable salts and solvates (e.g. hydrates) may be prepared by the general methods outlined hereinafter. In the following processes, R_1, R_2, R_3, R_4, A, and Alk are as defined for the general formula (I) unless otherwise specified.

According to a general process (A), compounds of general formula (I) may be prepared by cyclisation of compounds of general formula (II) :



(II)

wherein Q is the group NR_3R_4 or a protected derivative thereof or a leaving group such as a halogen atom (e.g. chlorine or bromine), or an acyloxy group which may be derived from a carboxylic or sulphonic acid, such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, *p*-nitrobenzoyloxy, *p*-toluenesulphonyloxy or methanesulphonyloxy group. The reaction may conveniently be effected in aqueous or non-aqueous reaction media, and at temperatures of from 20 to 200°C, preferably 50 to 125°C.

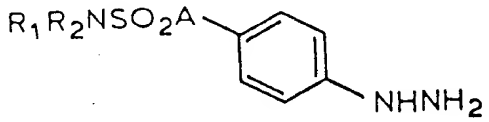
Particularly convenient embodiments of the process are described below.

When Q is the group NR_3R_4 (or a protected derivative thereof) the process is desirably carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in "Reagents for Organic Synthesis", (Fieser and Fieser, John Wiley and Sons 1967).

Alternatively the cyclisation may be carried out in an aqueous or non-aqueous reaction medium, in the presence of an acid catalyst. When an aqueous medium is employed this may be an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents and the acid catalyst may be, for example, an inorganic acid such as concentrated hydrochloric or sulphuric acid or an organic acid such as acetic acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise one or more alcohols or ethers (e.g. as previously described) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride.

When Q is a leaving group, such as a chlorine or bromine atom, the reaction may be effected in an aqueous organic solvent, such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran), in the absence of an inorganic acid catalyst, conveniently at a temperature of from 20 to 200°C, preferably 50 to 125°C. This process results in the formation of a compound of general formula (I) wherein R_3 and R_4 are both hydrogen atoms.

According to a particular embodiment of this process, compounds of general formula (I) may be prepared directly by the reaction of a compound of general formula (III):



(III)

or a salt (e.g. the hydrochloride) thereof, with a compound of formula (IV):

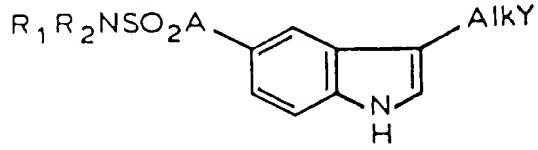
$$OHCCH_2AlkQ \qquad (IV)$$

(wherein Q is as previously defined) or a salt or protected derivative thereof (such as an acetal, for example, a dialkyl or cyclic acetal e.g. formed with an appropriate alkyl orthoformate or diol or protected as a bisulphite addition complex), using the appropriate conditions as just described for the cyclisation of a compound of general formula (II) (The Fischer-Indole Synthesis, B. Robinson, p 488 - Wiley 1982). In this embodiment compounds of general formula (II) may be formed as intermediates and they may either be isolated prior to cyclisation or reacted *in situ* to form the desired compounds of general formula (I).

Compounds of general formula (II) may, if desired, be isolated as intermediates by reacting a compound of formula (III), or a salt or protected derivative thereof with a compound of formula (IV) or a salt or protected derivative thereof, in a suitable solvent, such as an aqueous alcohol (e.g. methanol) or an aqueous ether (e.g. dioxan) and at a temperature of, for example, from 20 to 30°C. If an acetal of a compound of formula (IV) is used it may be necessary to carry out the reaction in the presence of an acid (for example, acetic or hydrochloric acid).

The compounds of general formula (III) are novel compounds and form a further aspect of this invention. The compounds of general formula (III) may be prepared using conventional methods for preparing a hydrazine, for example reduction of the corresponding nitro compound to form the amino derivative, by catalytic hydrogenation, followed by reaction with sodium nitrite in the presence of a mineral acid (e.g. hydrochloric acid) to form a diazonium salt which is then reduced, e.g. with stannous chloride, to the desired hydrazine of formula (III).

A further general process (B) for preparing compounds of general formula (I) comprises reacting a compound of general formula (V):



(V)

(wherein Y is a readily displaceable group) or a protected derivative thereof, with a compound of formula R_3R_4NH.

This displacement reaction may conveniently be carried out on those compounds of general formula (V) wherein the substituent group Y is a halogen atom (e.g. chlorine, bromine or iodine); a group OR_5 where OR_5

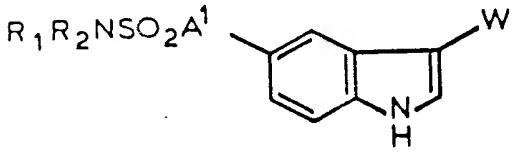
is, for example, an acyloxy group (which may be derived from a carboxylic or sulphonic acid) such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy or *p*-nitrobenzoyloxy, *p*-toluenesulphonyloxy or methanesulphonyloxy group; or a group $\overset{\oplus}{N}R'R''R'''\overset{\ominus}{E}$, where R', R'' and R''', which may be the same or different each represents a C_{1-3} alkyl group and $\overset{\ominus}{E}$ represents an anion such as a halide ion e.g. a chloride, bromide or iodide ion.

The displacement reaction may conveniently be effected in an inert organic solvent (optionally in the presence of water), examples of which include alcohols e.g. ethanol; cyclic ethers, e.g. dioxan or tetrahydrofuran; acyclic ethers, e.g. diethylether; esters e.g. ethyl acetate; amides e.g. N,N-dimethylformamide; and ketones e.g. acetone, methylethylketone or methylisobutylketone. The process may be carried out at a temperature of, for example, −10 to +150°C, preferably 20 to 50°C.

The compounds of formula (V) wherein Y is a halogen atom may be prepared by reacting a hydrazine of formula (III) with an aldehyde (or a protected derivative thereof) of formula (IV) in which Q is a halogen atom, in an aqueous alcohol (e.g. methanol) or an aqueous ether (e.g. dioxan) containing an acid (e.g. acetic or hydrochloric acid) or by reacting a compound of general formula (V) wherein Y is a hydroxy group with the appropriate phosphorus trihalide or with N-bromosuccinimide and triphenylphosphine in tetrahydrofuran. The intermediate alcohol, wherein Y is a hydroxy group, may also be used to prepare compounds of formula (V), wherein Y is a group OR_5, by acylation with the appropriate activated species (e.g. an anhydride or sulphonyl chloride) using conventional techniques. The intermediate alcohol may be prepared by cyclisation of a compound of formula (II) wherein Q is a hydroxyl group (or a protected derivative thereof) under standard conditions.

Compounds of formula (V) wherein Y represents a group $\overset{\oplus}{N}R'R''R'''\overset{\ominus}{E}$ may be prepared from the corresponding tertiary amine by reaction with an alkylating agent, for example as described in general process (E) hereinafter.

Compounds of general formula (I) may also be prepared by another general process (C) involving reduction of a compound of general formula (VI) :



(VI)

wherein W is a group capable of being reduced to give the required $AlkNR_3R_4$ group or to give a protected derivative of the $AlkNR_3R_4$ group, and A^1 represents the group A as previously defined or a group capable of being reduced to form the group A, or a salt or protected derivative thereof.

Groups A^1 which may be reduced to give the required group A include corresponding unsaturated groups such as C_{2-6}-alkenyl groups.

The required Alk and NR_3R_4 groups may be formed by reduction steps which take place separately or together in any appropriate manner.

Groups which may be reduced to the group Alk include corresponding unsaturated groups and corresponding groups containing one or more hydroxyl groups or carbonyl functions.

Groups which may be reduced to the group NR_3R_4 include nitro, azido, hydroxyimino, nitrile and amide groups.

Examples of groups represented by the substituent group W thus include TNO_2 (where T is Alk or an alkenyl group corresponding to the group Alk); $AlkN_3$; $AlkNR_3COR'_4$; $-COCONR_3R_4$; $(CHR_8)_xCHR_6CN$; CHR_6COZ; $(CHR_8)_xCR_6{=}NOH$; $CH(OH)CHR_6NR_3R_4$; $COCHR_6Z$ (where R_8 and R_6 which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, Z is an azido group N_3 or the group NR_3R_4 or a protected derivative thereof, *x* is zero or 1 and R_4' is a hydrogen atom or a group such that $-CH_2R_4'$ is the group R_4, or R_4' is the group OR_7 where R_7 is an alkyl or an aralkyl group).

Groups which may be reduced to form the group NR_3R_4 wherein R_3 and R_4 are both hydrogen include nitro, azido, hydroxyimino and nitrile groups. Reduction of a nitrile group yields the group CH_2NH_2 and thus provides a methylene group of the group Alk.

A compound of general formula (I) where R_4 is a hydrogen atom, may also be prepared by reduction of a corresponding compound of general formula (I) wherein R_4 is a benzyl group, for example with hydrogen in the presence of a catalyst e.g. 10% palladium on carbon.

The required NR_3R_4 group wherein R_3 and/or R_4 is other than hydrogen may be prepared by reduction of a nitrile $(CHR_8)_xCHR_6CN$ or an aldehyde $(CHR_8)_xCHR_6CHO$ (where R_8, R_6 and *x* are previously defined) in the presence of an amine, R_3R_4NH.

A particularly suitable method for preparing a compound of formula (I) wherein R_3 and/or R_4 is other than hydrogen, is reductive alkylation of the corresponding compound wherein R_3 and/or R_4 represents hydrogen, with an appropriate aldehyde or a ketone (e.g. formaldehyde or acetone) in the presence of a suitable reducing agent. In some instances (e.g. for the introduction of the group R_4 where R_4 is methyl) the aldehyde (e.g. formaldehyde) may be condensed with the primary amine and the intermediate thus formed may subsequently be reduced using a suitable reducing agent.

The required NR_3R_4 group wherein R_3 and/or R_4 are other than hydrogen may also be prepared by reduction of a corresponding amide, for example $AlkNR_3COR_4'$ (where R_4' is as previously defined).

The reduction may be effected by conventional methods, for example by catalytic hydrogenation or using a reducing agent such as an alkali metal or alkaline earth metal borohydride or cyanoborohydride , or a metal hydride. The reduction may conveniently be effected in an organic reaction medium which may comprise one or more solvents. Suitable solvents include alcohols e.g. ethanol or propanol; cyclic eters e.g. dioxan or tetrahydrofuran; acrylic ethers e.g. diethylether; amides e.g. dimethylformamide; and esters e.g. ethyl acetate, and nitriles e.g. acetonitrile.

It will be appreciated that the choice of reducing agent and reaction conditions will be dependent on the nature of the groups W and A^1.

Suitable reducing agents which may be used in the above process for the reduction of compounds of formula (VI) wherein W represents, for example, the groups TNO_2, $AlkN_3$, $(CHR_5)_xCHR_6CN$, $(CHR_5)_xCR_6{=}NOH$, $CH(OH)CHR_6{-}NR_3R_4$ (where T, R_5 and R_6 and x are as previously defined) include hydrogen in the presence of a metal catalyst, for example Raney Nickel or a noble metal catalyst such as platinum, platinum oxide, palladium or rhodium, which may be supported, for example, on charcoal, kieselguhr or aluminia. In the case of Raney Nickel, hydrazine may also be used as the source of hydrogen. This process may conveniently be carried out in a solvent such as an alcohol e.g. ethanol; an ether, e.g. dioxan or tetrahydrofuran; an amide, e.g. dimethylformamide;or an ester e.g. ethyl acetate, and at a temperature of from −10 to +50°C, preferably −5 to +30°C.

The reduction process may also be effected on compounds of general formula (VI) wherein W represents, for example, the groups TNO_2, $CH(OH)CHR_6NR_3R_4$ or $COCHR_6$ (where T, R_6 and Z are as previously defined), using an alkali metal or alkaline earth metal borohydride or cyanoborohydride e.g. sodium or calcium borohydride or cyanoborohydride which process may conveniently be carried out in an alcohol such as propanol or ethanol, or a nitrile such as acetonitrile, and at a temperature of from 10 to 100°C, preferably 50 to 100°C. In some instances the reduction using a borohydride may be carried out in the presence of cobaltous chloride.

Reduction of compounds of general formula (VI) wherein W represents, for example, the groups TNO_2, $AlkN_3$, $AlkNR_3COR_4'$, CHR_6COZ, $(CHR_5)_xCR_6{=}NOH$, $CH(OH)CHR_6{-}NR_3R_4$, $-COCONR_3R_1$ and $COCHR_6Z$ (wherein T, R_4', R_5, R_6, Z and x are as previously defined) may also be carried out using diborane or a metal hydride such as lithium aluminium hydride. This process may be carried out in a solvent, for example, an ether such as tetrahydrofuran, and conveniently at a temperature of from −10 to +100°C, preferably 50 to 100°C.

A particular embodiment of general process (C) includes the reduction of a compound of general formula (VI) wherein W is the group CHR_6CN, for example, by catalytic reduction with hydrogen in the presence of a catalyst such as palladium on charcoal or rhodium on alumina, optionally in the presence of an amine HNR_3R_4, or, to produce a compound wherein R_3 and R_4 are both hydrogen, using lithium aluminium hydride in the absence of an amine.

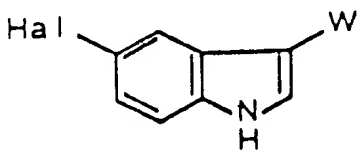
Suitable reducing agents which may be used in the reduction of the group A^1 include hydrogen in the presence of a metal catalyst. Appropriate metal catalysts and conditions for the process are as described for the reduction of the group W.

The starting materials or intermediate compounds of general formula (VI) may be prepared by analogous methods to those described in U.K. Published Patent Application No. 2036310 and "A Chemistry of Heterocyclic Compounds - Indoles Part II" Chapter VI edited by W.J. Houlihan (1972) Wiley Interscience, New York.

A compound of general formula (VI) wherein W is the group $AlkNHCOR_4'$ may be prepared by acylation of the corresponding unsubstituted amine using conventional techniques.

The Fischer-Indole cyclisation process may be employed to prepare a compound of general formula (VI) wherein W is the group $(CHR_5)_xCHR_6CN$ or $CHR_5CHR_6NO_2$ in conventional manner.

A compound of formula (VI) where in A^1 is an alkenyl group containing 2 to 5 carbon atoms may be prepared by reacting a corresponding 5-halo indole of general formula (VII) :

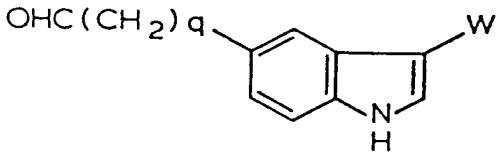


(VII)

wherein W is as defined for general formula (VI) and

Hal is a halogen atom e.g. bromine or iodine, with an appropriate alkene of formula $R_1R_2NSO_2(CH_2)_pCH{=}CH_2$ (wherein p represents zero or 1 to 3) in the presence of a catalyst such as a palladium (II) salt, for example the acetate and a phosphine e.g. triphenylphosphine or tri-*o*-tolylphosphine, together with a tertiary nitrogen base such as triethylamine or tri-*n*-butylamine. The reaction may conveniently be effected in a solvent, e.g. acetonitrile, methanol or dimethylformamide, and at a temperature of from 75 to 160°C. Alternatively, compounds of formula (VI) may be prepared by reaction of an

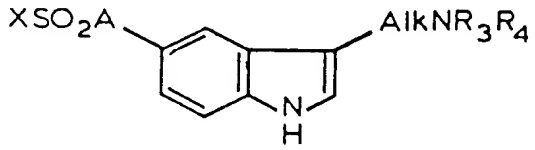
appropriate indole-5-carboxaldehyde of general formula (VIIII) :



(VIII)

wherein W is as defined for general formula (VI) and q is an integer of 1 to 4, with for, example, a suitable dialkylphosphonate, using standard conditions.

Compounds of general formula (I) may be prepared by another general process (D) which comprises reacting an indole of general formula (IX) :



(IX)

wherein X represents a leaving group with an amine of general formula (X) :

(X)

Examples of suitable leaving groups X in the compound of general formula (IX) include a halogen atom (e.g. a fluorine, chlorine or bromine atom) or a group OR_7, where R_7 represents a hydrocarbyl group such as an aryl group, e.g. phenyl. The aryl may be unsubstituted or substituted by one or more substituents such as halogen atoms; or nitro; cyano; amino; alkyl e.g. methyl; alkoxy e.g. methoxy; acyl, e.g. acetyl and alkoxycarbonyl e.g. ethoxycarbonyl groups. The leaving group represented by X is preferably a phenoxy group.

The reaction is conveniently carried out in the presence of a solvent and may be effected in an aqueous or non-aqueous reaction medium.

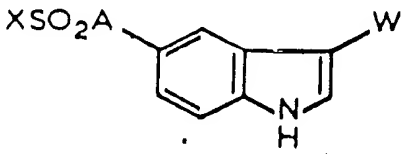
The reaction medium may thus comprise one or more organic solvents, such as ethers, e.g. dioxan or tetrahydrofuran; amides e.g. N,N-dimethylformamide or N-methylpyrrolidone; alcohols e.g. methanol or ethanol; esters e.g. ethyl acetate; nitriles e.g. acetonitrile; halogenated hydrocarbons e.g. dichloromethane; and tertiary amines e.g. triethylamine or pyridine, optionally in the presence of water. In some cases the amine of formula (X) may itself serve as the solvent.

If desired the aminolysis may be effected in the presence of a base, such as a tertiary amine (e.g. triethylamine or pyridine); an alkoxide (e.g. sodium t-butoxide) or a hydride (e.g. sodium hydride).

The reaction may conveniently be effected at a temperature of from −20°C to +150°C.

The compounds of general formula (IX) are novel compounds and constitute a further aspect of this invention. They possess potent and selective vasoconstrictor activity, as described above for compounds of general formula (I).

The starting materials of general formula (IX) wherein X represents a group OR_7 may be prepared, for example by reduction of a compound of general formula (XI)



(XI)

(wherein W is as defined for general formula VI)) or a salt or protected derivative thereof.

The reduction may be carried out in analogous manner to the general process (C) and examples of suitable groups W and details of reaction conditions are given in connection with the general process (C).

A compound of formula (IX) wherein X represents a halogen atom may be prepared, for example by reacting the corresponding sulphonic acid derivative or a salt thereof with a halogenating agent such as a phosphorus halide or oxyhalide in an inert organic solvent e.g. phosphorus pentachloride in dichloromethane. A sulphonic acid of formula (IX), where X is OH, may be prepared for example by acid or base catalysed hydrolysis of an ester of formula (IX) (i.e. a compound wherein X represents the group OR_7).

Compounds of general formula (XI) may be prepared by analogous methods to those described in U.K. Published Patent Application No. 2035310 and "A Chemistry of Heterocyclic Compounds - Indoles Part II"

Chapter VI edited by W.J. Hamilton (1972) Wiley Interscience, New York, as well as our copending U.K. Patent Application No. 8315564.

According to a further general process (E) a compound of formula (I) according to the invention, or a salt or protected derivative thereof may be converted into another compound of the invention using conventional procedures.

For example, a compound of general formula (I) wherein one or more of R_1, R_2, R_3 and R_4 are alkyl groups may be prepared from the corresponding compounds of formula (I) wherein one or more of R_1, R_2, R_3 and R_4 represent hydrogen atoms, by reaction with a suitable alkylating agent such as a compound of formula R_xL where R_x represents the desired R_1, R_2, R_3 or R_4 group and L represents a leaving group such as a halogen atom or a tosylate group, or a sulphate $(R_x)_2SO_4$. Thus, the alkylating agent may be for example and alkyl halide (e.g. methyl or ethyl iodine), alkyl tosylate (e.g. methyl tosylate) or dialkylsulphate (e.g. dimethylsulphate). The alkylation reaction is conveniently carried out in an inert organic solvent such as an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides, such as sodium or potassium hydride, alkali metal amides, such as sodium amide, alkali metal carbonates, such as sodium carbonate and alkali metal alkoxides such as sodium or potassium methoxide, ethoxide or t-butoxide. When an alkyl halide is employed as the alkylating agent the reaction may also be carried out in the presence of an acid scavenger such as propylene or ethylene oxide. A catalyst such as tetrabutylammonium fluoride may also be employed. The reaction may be conveniently effected at a temperature of −20°C to +100°C.

Compounds of formula (I) wherein R_1 represents a C_{3-6} alkenyl group, R_2 represents a C_{3-6} alkenyl, phen(C_{1-4})alkyl or C_{5-7} cycloalkyl group and /or one or both of R_3 and R_4 represents propenyl may be prepared similarly, using an appropriate compound of formula R_xL or $(R_x)_2SO_4$.

According to another general process (F), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the reaction sequence for the preparation of a compound of general formula (I) or a salt thereof it may have been necessary or desirable to protect one or more sensitive groups in the molecule to avoid undesirable side reactions. For example it may be necessary to protect the group NR_3R_4, wherein R_3 and/or R_4 represents hydrogen, by protonation or with a group easily removable at the end of the reaction sequence. Such groups may include, for example, aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl; or acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl.

In some cases, it may also be desirable to protect the indole nitrogen with, for example, an aralkyl group such as benzyl.

Subsequent cleavage of the protecting group or groups may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal) or sodium and liquid ammonia; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation. The phthaloyl group may be removed by hydrazinolysis (e.g. by treatment with hydrazine hydrate) or by treatment with a primary amine (e.g. methylamine).

As will be appreciated, in some of the general processes (A) to (E) described previously it may be necessary or desirable to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the previously described processes (A) to (E).

Thus, according to a further aspect of the invention, the following reactions (G) in any appropriate sequence may if necessary and/or desired be carried out subsequent to any of the processes (A) to (E) :

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate (e.g. hydrate) thereof.

Where it is desired to isolate a compound of the invention as a physiologically acceptable salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I), with an appropriate acid (e.g. succinic or hydrochloric acid) preferably with an equivalent amount in a suitable solvent (e.g. aqueous ethanol).

The starting materials or intermediate compounds for the preparation of the compounds according to this invention may be prepared by conventional methods analogous to those described in U.K. Published Patent Application No. 2035310.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5-position may be introduced either before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following examples. All temperatures are in °C. 'Hyflo' is a filtration aid. Reactivials are 4ml stout-walled glass vials with a screw cap and teflon-faced disc, supplied by

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Compounds of formula (I) wherein R_1 represents a C_{3-6} alkenyl group, R_2 represents a C_{3-6} alkenyl, phen(C_{1-4})alkyl or C_{5-7} cycloalkyl group and /or one or both of R_3 and R_4 represents propenyl may be prepared similarly, using an appropriate compound of formula R_{xL} or $(R_x)_2SO_4$.

According to another general process (F), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (II) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the reaction sequence for the preparation of a compound of general formula (I) or a salt thereof it may have been necessary or desirable to protect one or more sensitive groups in the molecule to avoid undesirable side reactions. For example it may be necessary to protect the group NR_3R_4, wherein R_3 and/or R_4 represents hydrogen, by protonation or with a group easily removable at the end of the reaction sequence. Such groups may include, for example, aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl; or acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl.

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As will be appreciated, in some of the general processes (A) to (E) described previously it may be necessary or desirable to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the previously described processes (A) to (E).

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The starting materials or intermediate compounds for the preparation of the compounds according to this invention may be prepared by conventional methods analogous to those described in U.K. Published Patent Application No. 2035310.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5-position may be introduced either before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following examples. All temperatures are in °C. 'Hyflo' is a filtration aid. Reactivials are 4ml stout-walled glass vials with a screw cap and teflon-faced disc, supplied by

Pierce and Warriner (UK) Ltd. Chromatography was carried out either in the conveniental manner using silica gel (Merck, Kieselgel 60, Art. 7734) or by 'flash' chromatography (W. C. Still, M. Kahn and A. Mitra, J. Org. Chem. 2923, *43*, 1978) on silica (Merck 9385) and thin layer chromatography (t.l.c) on silica (Macherly-Nagel, Polygram) except where otherwise stated. The following abbreviations define the eluent used for chromatography and t.l.c.

(A) Methylene chloride-ethanol-0.88 ammonia 50:8:1
(B) Methylene chloride-ethanol-0.88 ammonia 100:8:1
(C) Methylene chloride-ethanol-0.88 ammonia 60:8:1
(D) Methylene chloride-ethanol-0.88 ammonia 25:8:1
(E) Methylene chloride-ethanol-0.88 ammonia 200:8:1
(F) Methylene chloride-ethanol-0.88 ammonia 750:10:1
(G) Methylene chloride-ethanol-0.88 ammonia 40:10:1
(H) Ether-cyclohexane 1:1
(I) Methanol-chloroform 5:95
(J) Ether
(K) Methylene chlorine-ether 1:1
(L) Methylene chloride-ethanol-0.88 ammonia 75:8:1
(M) Isopropyl acetate
(N) Ethyl acetate-ether 1:1
(O) Methylene chloride-ethanol-0.88 ammonia 83.5:15:1.5
(P) Acetic acid-ethyl acetate 1:99
(Q) Ethyl acetate-cyclohexane 1:1
(R) Chloroform-methanol 50:1
(S) Chloroform-methanol 19:1
(T) Methylene chloride-ethanol-0.88 ammonia 150:8:1
(U) Methylene chloride-ethanol-0.88 ammonia 89:10:1
(V) Petroleum ether (bp60-80°)-ethylacetate 2:1
(W) Cyclohexane-ether 2:1

Intermediates were routinely checked for purity by t.l.c. employing u.v. light for detection and spray reagents such as potassium permanganate ($KMnO_4$). In addition indolic intermediates were detected by spraying with aqueous ceric sulphate (Ce^{IV}) and tryptamines by spraying with a solution of iodoplatinic acid (IPA) or ceric sulphate.

Proton (^1H) nuclear magnetic resonance (n.m.r) spectra were obtained either at 90MHz using a Varian EM 390 instrument or at 250MHz using a Bruker AM or WM 250 instrument. s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Preparation 1

N-Methyl-4-nitrobenzeneethanesulphonamide hydrate (4:1)

A solution of 4-nitrobenzeneethanesulphonyl chloride (6.5g) in methylene chloride (50ml) was added dropwise, over a period of 0.25h, to a rapidly stirred, ice-cold mixture of 40% aqueous methylamine (4ml) in methylene chloride (20 ml). Further portions of 40% aqueous methylamine (1ml) were added after stirring the suspension at 0° for a further 1h and 0.5h respectively. The suspension was then stirred at 0° for a further 0.5h, before evaporating under reduced pressure to afford a solid (*ca* 7.0g). This material was triturated with water (100ml) and the solid collected by filtration, washed with petroleum-ether (b.p. 60-80°) (50ml) and dried to present the *title compound* as a powder (5.46g) m.p. 126-129°.

Analysis Found: C,43.35; H,4.9; N,11.1

$C_9H_{12}N_2O_4S.0.25H_2O$ requires C,43.45; H,5.1; N,11.3%.

Preparation 2

4-Amino-N-methylbenzeneethanesulphonamide

A solution of the product of Preparation 1 (7.9g) in ethanol (150ml) and dimethylformamide (10ml) was added to a preroduced suspension of 10% palladium oxide on charcoal (1.0g, 50% aqueous paste) in ethanol (50ml) and hydrogenated at atmospheric pressure. After 2.75h a further portion of catalyst (1.0g) was added and the hydrogenation continued for another 2h. A total of 2.14 l of hydrogen was absorbed. The catalyst and solvent were removed, by filtration and rotary evaporation respectively, and the residual solid (8g) extracted with boiling ethyl acetate (3 × 50ml). The combined hot extracts were filtered and evaporated to dryness under reduced pressure to produce a solid. This material was triturated with petroleum-ether (b.p. 60-80°) to present the *title compound* as a powder (5.2g) m.p. 101-105°.

Preparation 3
4-Hydrazino-N-methylbenzeneethanesulphonamide hydrochloride

The product of Preparation 1 (1.0g) suspended in water (6ml) was treated with conc. hydrochloric acid (10 ml) which precipitated the hydrochloride salt. The mixture was then cooled to −5° and treated with sodium nitrite (0.38g) in water (2ml) and stirred for 50 minutes keeping the temperature below −5°. The suspension was rapidly filtered to remove unreacted starting material and the filtrate added slowly to stannous chloride (5.0g) in conc. hydrochloric acid (10ml) at −5°. The solution was allowed to warm to 20° with vigorous stirring and the precipitate that formed was collected and washed with ether (50 ml) to give the *title compound* (1.2g, 66% pure) as a powder. T.l.c. (A) Rf 0.8 (IPA)

Preparation 4
4-[2-(3-Cyanopropylidene)hydrazino]-N-methyl-benzeneethanesulphonamide

To a filtered solution of the product of Preparation 3 (0.6g, 67% pure) in water (13ml) and dilute hydrochloric acid (2N, 0.25ml) was added 3- cyanopropanal, dimethyl acetal (0.23g) and the resulting solution stirred at room temperature for 24h. The precipitated solid was filtered off, washed with water (2×30ml), diethyl ether (50ml) and dried to give the *title compound* as a powder (0.3g), m.p. 96-97°.

Preparation 5
3-(Cyanomethyl)-N-methyl-1H-indole-5-ethanesulphonamide

A suspension of the product of Preparation 4 (0.25g) in polyphosphate ester (2.5g) and chloroform (5 ml) was heated at reflux for 5 min and then poured onto ice. The resulting suspension was stirred for 20min then extracted with chloroform (4×10ml). The extract was washed with 8% sodium bicarbonate (10ml) and water (10ml), dried, filtered and evaporated to give an oil (0.35g). This oil was chromatographed (J) to give the *title compound* (0.06g) as an oil. T.l.c. (J) Rf 0.5 (u.v.).

Example 1
3-(2-Aminoethyl)-N-methyl-1H-indole-5-ethanesulphonamide hemisuccinate
Method (l)

A solution of the product of Preparation 3 (1.019g) in methanol (25ml) and water (5ml) was stirred at 50° and 4-chlorobutanal dimethylacetal (0.117g) was added. After stirring for 0.75h at 50° a further portion of 4-chlorobutanal dimethylacetal (0.117g) was added and stirring at 50° continued for another 0.75h. The solution was adjusted to pH4 by adding ammonium acetate (0.3g) and refluxed for 5h. Solvent was removed by evaporation under reduced pressure and the residue treated with saturated aqueous potassium carbonate solution (15ml) and extracted with ethyl acetate (4×50ml). The extracts were dried ($MgSO_4$) and concentrated to a gum (0.89g). This material was chromatographed (B), (C) to give the tryptamine free base as a gum (0.072g), which was taken up in hot isopropanol (2ml) and treated with a hot solution of succinic acid (0.0151g) in hot isopropanol (0.5ml). After adding absolute alcohol (*ca.* 1.0ml) to the boiling mixture the solution was allowed to cool. The solid that crystallised out was collected by filtration, washed with anhydrous ether and dried to present the *title compound* as a powder (0.046g) m.p. 133-138°.

Analysis Found: C,50.8;H,6.1;N,11.4
$C_{13}H_{19}N_3O_2S.0.5C_4H_6O_4.0.1C_3H_8.0.075H_2O$ requires: C,51.1;H,6.8;N,11.7%
N.m.r. δ(CD_3SOCD_3)2.65(3H,s,*Me*$NHSO_2$)2.7-3.4(8H,m,$NHSO_2CH_2CH_2$and$CH_2CH_2NH_2$),6.8-7.5(4H,m,aromatic).

Example 2
N-Methyl-3-[2-(methylamino)ethyl]1H-indole-5-ethanesulphonamide compound with succinic acid and water (6:4:3)

A solution of the product of Preparation 5 (0.45g) in ethanolic methylamine (25% w/v, 25ml) was hydrogenated over 10% palladium oxide on charcoal (0.8g, 50% aqueous paste) pre-reduced in ethanol (5ml). The catalyst was removed by filtration through 'hyflo' and the filtrate concentrated to give a gum (0.45g) which was dissolved in hot isopropanol (5ml) and treated with a solution of succinic acid (0.093g) in methanol (0.5ml). A thick gum precipitated out. The reaction mixture was concentrated in vacuo (ca. 1ml of solvent). The solvent was decanted off and the residual gum was triturated with diethyl ether (3×25ml) to give a solid which was filtered off and dried to give the *title compound* as a powder 0.33g, m.p. 62-65°.

Analysis Found: C,52.5;H,6.8;N,11.0
$C_{14}H_{21}N_3O_2S.0.66C_4H_6O_2.0.5H_2O$ requires C,52.3;H,7.2;N,10.9%.
nmr spectrum agreed with that of Example 3.

Example 3

N-Methyl-3-[2-(methylamino)ethyl]-1H-indole-5-ethanesulphonamide hydrochloride

In a similar manner to Example 2 the product of Preparation 5 (0.70g) was hydrogenated, filtered and the filtrate concentrated to give a gum (0.7g) which was purified by flash chromatography (T, 3cm dia. col). The resulting gum (0.3g) was extracted with ethyl acetate (20ml), filtered and treated with an excess of ethereal hydrogen chloride. The solid was collected by filtration, washed with ether (25ml) and dried (15h, 20°, vacuum pistol) to give the *title compound* as a powder, (0.24g) m.p. 151-154°.

Analysis Found: C,49.3;H,6.6;N,11.8.

$C_{14}H_{21}N_3O_2S.HCl.0.5H_2O.0.07C_4H_8O_2$ requires C,49.3;H,6.8;N,12.1.

nmr δ (CD_3SOCD_3)2.50 (3H, sNH*Me*) 2.66 (3H, s SO_2NHMe) 2.9-3.5 (8H, m$CH_2CH_2SO_2NH$ andCH_2CH_2NH) and 6.9-7.5 (m aromatic).

Example 4

3-(2-Aminoethyl)-N-(phenylmethyl)-1H-indole-5-ethanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1)

(i) *4-Nitro-N-(phenylmethyl)benzeneethanesulphonamide*

Benzylamine (9.83ml) in duchloromethane (10ml) was added dropwise to an ice-cold, stirred solution of 4-nitrobenzeneethanesulphonyl chloride (7g) in dichloromethane (250ml). After 18h the reaction mixture was washed with water (3×40ml), brine (3×25ml), dried (Na_2SO_4)and evaporated to dryness and the product recrystallised from isopropanol (50ml) to give the *title compound* as needles (6g), m.p. 125-127°C.

(ii) *4-Amino-N-(phenylmethyl)benzeneethanesulphonamide*

A suspension of the product of Stage (i) (11g) in methanol (120ml) was hydrogenated over pre-reduced 10% palladium oxide on charcoal (50% aq. paste, 2g) at room temperature and pressure until hydrogen uptake (1.99ℓ) ceased. The catalyst was filtered off and the filtrate evaporated to dryness to give a solid which was purified by crystallisation from methanol to give the *title compound* as a solid (3.2g) m.p. 109-111°.

T.l.c. (E) Rf 0.4 (Ce^{IV}).

(iii) *4-Hydrazino-N-(phenylmethyl)benzeneethanesulphonamide, hydrochloride*

A solution of sodium nitrite (0.25g) in water (1.9ml) was added to a cold suspension of the product of Stage (ii) (1g) in a mixture of conc. hydrochloric acid (7.5ml) and water (4.5ml) keeping the temperature below −5°C. This mixture was stirred at −5° for 50min and the remaining solid removed by filtration. The ice-cooled filtrate was then added slowly to a solution of stannous chloride dihydrate (3.5g) in conc. hydrochloric acid (7.5ml) keeping the temperature below 0°. After the addition the mixture was stirred at room temperature for 3h and the solid collected, washed with diethyl ether (3×50ml) and dried to give the *title compound* as a powder (0.46g).

T.l.c. (B) Rf 0.43(IPA).

(iv) *3-(2-Aminoethyl)-N-(phenylmethyl)-1H-indole-5-ethanesulphonamide compound with creatinine, sulphuric acid and water (1:1:1:1)*

4-Chlorobutanal dimethyl acetal (0.18g) was added to a stirred solution of the product of Stage (iii) (0.45g) in a mixture of ethanol (18ml) and water (4.5ml) and the mixture heated at reflux for 2h. The cooled mixture was evaporated to dryness and the residue chromatographed twice (A) to give the tryptamine as an oil (70mg) which was dissolved in a boiling mixture of ethanol (5.6ml) and water (0.7ml) and treated with an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.1ml). On cooling the *title compound* was deposited as a solid (96mg) m.p. 217-220° (softens at 210°).

Analysis Found: C,47.0;H,6.9;N,14.2.

$C_{19}H_{23}N_3O_2S.C_4H_7N_3O.H_2SO_4.H_2O$ requires C,47.1;H,6.8;N,14.3%.

N.m.r. δ(CD_3SOCD_3)2.9-3.3(8H,m,$NHSO_2CH_2CH_2$ and $CH_2CH_2NH_2$),4.24 (2H,s,CH_2NHSO_2),6.85-7.5(m,aromatic).

Example 5

3-[2-(Ethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hemisuccinate hemihydrate

Method (i) A suspension of 10% palladium oxide on carbon (0.8g of a 50% paste with water) in ethanol (5ml) was prehydrogenated for 20min. To this was added the product of Preparation 5 (0.40g) in ethanolic ethylamine (25ml) and the resulting suspension was stirred for 2h at 20°. The suspension was filtered through hyflo and the filtrate concentrated *in vacuo* to give an oil (0.38g) which was chromatographed twice (B) to give the triptamine as an oil (0.114g). The oil was dissolved in absolute ethanol (2ml) and to this was added succinic acid (22.5mg) in ethanol. The crystals were collected by filtration to give the *title compound* (70mg) m.p. 148-150°.

Analysis Found: C,54.5;H,7.1;N,10.9

$C_{15}H_{23}N_3O_2S.0.5C_4H_6O_4.0.5H_2O$ requires C,54.1;H,7.2;N,11.1%.

N.m.r. δ(CD_3SOCD_3)1.11(3H,t,$NHCH_2Me$),2.64(3H,s.*Me*$NHSO_2$),2.78(2H,q,$NHCH_2CH_3$),2.85-3.4(8H,m,$NHSO_2CH_2CH_2$, and CH_2CH_2NH)6.9-7.5(4H,m, aromatic).

Method (II)

(i) *N-[2-[5-[2-[(Methylamino)sulphonyl]ethyl]-1H-indol-3-yl]ethyl]acetamide*

A solution of the product of Example 1 (0.3g) in anhydrous tetrahydrofuran (15ml) was treated with acetic anhydride (0.084ml) and stirred at room temp. for 1.5h. The resulting solution was then evaporated to dryness and the residue dissolved in ethyl acetate (20ml). The ethlyl acetate solution was washed with aqueous 8% sodium bicarbonate (20ml) and then with water (10ml) dried and evaporated under reduced pressure to produce a gum (0.45g). This material was chromatographed (A) to give the *title compound* as a gum (0.389g).

T.l.c. (A) Rf 0.6.

(ii) *3-[2-(Ethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hemisuccinate*

A solution of the product of Stage (i) (0.3g) in anhydrous tetrahydrofuran (THF) (16ml) was added to a stirred mixture of lithium aluminium hydride (0.353g) in THF (20ml) under an atmosphere of nitrogen. The resulting suspension was stirred for 2h at reflux and then allowed to stand overnight at room temp. before refluxing for a further 1h. After cooling the reaction (ice-bath), water (10ml) was added and the resulting mixture filtered through hyflo. The filtrate was extracted with ethyl acetate (4 × 25ml) and the extracts dried ($MgSO_4$) and evaporated to produce a gum (0.187g). This material was chromatographed (A) to give the free base as a gum (0.12g). A solution of the free base (0.12g) in hot absolute alcohol (2ml) was treated with a solution of succinic acid (0.0229g) in methanol (0.75ml). The resulting solution was evaporated to dryness to yield a foam which was triturated with anhydrous ether to present the *title compound* as a hygroscopic foam (0.068g) m.p. 65-75°, shown by n.m.r. and t.l.c.(B,Rf 0.25) to be identical with the product of Method (I).

Example 6

3-(3-Aminopropyl)-N-methyl-1H-indole-5-ethanesulphonamide compound with oxalic acid and ethanol (1:1.2:0.83)

(i) *3-[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-N-methyl-1H-indole-5-ethanesulphonamide*

A mixture of the product of Preparation 3 (68% pure; 2.5g) and 2-(5,5-dimethyoxypentyl)-1*H*-isoindole-1,3(2*H*)-dione (83%pure; 3.15g) in 10% aqueous acetic acid (200ml) was stirred at room temperature for 1.75h, and then at reflux for 3.5h. The mixture was allowed to cool, extracted with chloroform (3×100ml) and the combined extracts washed with 2N hydrochloric acid (100ml) and 2N sodium carbonate (100ml), dried (Na_2SO_4) and concentrated *in vacuo*. Short-path column chromatography (F, 15cm dia. col.) of the residual gum (4.33g) afforded a solid (0.43g). Crystallisation of this solid from a mixture of chloroform and methanol (1:1, 10ml) gave the *title compound* as a solid (0.25g) m.p. 169-169.5°

T.l.c. (F) Rf 0.19 (Co^{IV}).

(ii) *3-(3-Aminopropyl)-N-methyl-1H-indole-5-ethanesulphonamide compound with oxalic acid and ethanol (1:1.2:0.83)*

Hydrazine hydrate (0.34ml) was added to a refluxing suspension of the product of Stage (i) (250mg), in ethanol (10ml), the resultant solution stirred for 4h, and then allowed to cool. The suspension was concentrated *in vacuo* and the residual solid partitioned between 2N sodium carbonate (25ml) and ethyl acetate (3×25ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (G, 1cm, dia. col.) of the residue (110mg) afforded a gum (98mg) which was dissolved in refluxing absolute ethanol (3ml) and a solution of oxalic acid (30mg) in absolute ethanol (0.5ml) was added. The gummy suspension was warmed gently to obtain a solution and allowed to cool with stirring. The resultant suspension was filtered, and the solid washed with absolute ethanol (3×1ml) and dried *in vacuo* at 50° for 18h to give the *title compound* as a solid (110mg) m.p. 160-162° (softens > 98°)

Analysis Found: C,49.2;H,6.85;N,9.6. $C_{14}H_{21}N_3O_2S.1.2C_2H_2O_4.0.83C_2H_6O$ requires C,49.1;H,6.5;N,9.5%.

N.m.r. δ(CD_3SOCD_3)1.90(2H,m,$CH_2CH_2CH_2NH_2$),2.62(3H,d,$MeNHSO_2$),2.73 and 2.82(4H,t and t,$CH_2CH_2CH_2NH_2$),2.95-3.3(4H,m,$NHSO_2CH_2CH_2$),6.95-7.45 (4H,m,aromatic).

Example 7

3-(2-Aminopropyl)-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride

(i) *4-Nitropentanal*

To a cold solution of acrolein (45ml) and nitroethane (120ml), in ether (750ml) was added a solution of tri-n-butylphosphine (15 drops) in ether (60ml) so that the temperature did not exceed − 8°. The reaction was stirred for a further 30min, methyl iodide (2 drops) was added and the ether was removed by evaporation *in vacuo* at 40°. The residue was purified by column chromatography (H) to give an oil (6.7g) which was distilled at 130-135°, 3mmHg to give the *title compound* as an oil (1.5g).

T.l.c; (H) Rf 0.3 ($KMnO_4$)

(ii) *N-Methyl-4-[2-(4-nitropentylidene)hydrazino]benzeneethanesulphonamide*

To a filtered solution of the product of Preparation 3 (3.678g of 67% purity) in water (20ml) was added dropwise 4-nitropentanal (1.5g) and the reaction was monitored by t.l.c. The reaction mixture was extracted with chloroform (200ml), dried ($MgSO_4$) and evapotated *in vacuo* to give the *title compound* (2.8g) as an oil which was used without further purification in the next stage.

T.l.c. (I) Rf 0.4 (Ce^{IV})

(iii) *N-Methyl-3-(2-nitropropyl)-1H-indole-5-ethanesulphonamide*

A solution of the product of Stage (ii) (2.8g) polyphosphate ester (28g) and chloroform (50ml) was heated at reflux for 5min and then poured onto ice (100g). The resulting suspension was stirred for 30min, and extracted with chloroform (3×100ml). The organic extract was washed with 8% sodium bicarbonate solution (2×100ml), water (2×100ml), dried ($MgSO_4$) filtered and evaporated to give an oil (5.2g). The oil was purified by flash chromatography (J, 8cm dia. col.) to give the *title compound* (0.47g) as an oil.

T.l.c. (J) Rf 0.8 ($KMnO_4$, IPA)

Analysis Found: C,51.5;H,5.6;N,12.7.

$C_{14}H_{19}N_3O_4S$ required C,51.7;H,5.9;N,12.9.

(iv) *3-(2-Aminopropyl)-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride*

A solution of the product of Stage (iii) (0.43g) in ethanol (50ml), was hydrogenated over pre-reduced 10% palladium oxide on charcoal (0.4) for 75.5h at atmospheric pressure and temperature. The reaction was filtered and evaporated *in vacuo* to give an oil (0.27g) which was chromatographed (A, 3cm dia. col.) to give the tryptamine as an oil (0.23g). A solution of the oil in ethanol (5ml) was treated with ethereal chloride (pH3), the salt filtered off and dried to give the *title compound* as a solid (0.2g) m.p. 211-212°.

Analysis Found: C,50.4;H,6.7;N,12.2.

$C_{14}H_{21}N_3O_2S.HCl.0.18H_2O$ requires C,50.2;H,6.7;N,12.5.

N.m.r. $\delta(CD_3SOCD_3)$1.19(3H,d,CH–CH_3),2.64(3H,d,SO_2NHCH_3),2.75-3.5(7H,m,CH_2CH(Me)NH_2 and $CH_2CH_2SO_2NH$),7-7.55(5H,m,aromatic + $NHSO_2$)

Example 8

3-(2-Aminoethyl)-N,N-dimethyl-1H-indole-5-ethanesulphonamide compound with creatinine and sulphuric acid (1:1:1)

(i) 2-(1H-Indol-5-yl)-N,N-dimethylethenesulphonamide

A mixture of 5-bromoindole (7.7g), N,N-dimethylethenesulphonamide (5.3g) triethylamine (15ml), acetonitrile (5ml), palladium (II) acetate (0.35g) and tri-o-tolyphosphine (0.95g) was heated at 100°C in an autoclave for 3h. The resulting cooled mixture was partitioned between hydrochloric acid (2N, 300ml) and ethyl acetate (2×150ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by 'flash' chromatography (V, 7cm col.) to give the *title compound* as a crystalline solid (3.6g) m.p. 148-150°C.

(ii) *N-N-Dimethyl-1H-indole-5-ethanesulphonamide*

A solution of the product of Stage (i) (3.8g) in ethanol (400ml) was hydrogenated at room temperature and pressure over 10% palladium oxide on charcoal (50% aq. paste, 0.5g), for 2h. The catalyst was filtered off and replaced with a fresh batch (50% aq. paste, 0.5g) and hydrogenation continued for a further 1h. The catalyst was filtered off and the filtrate evaporated *in vacuo* to give a solid (2.8g) which was recrystallised from a mixture of ethyl acetate and hexane to give the *title compound* as a solid (2.0g) m.p. 125-127°.

(iii) *3-[(Dimethylamino)methyl]-N,N-dimethyl-1H-indole-5-ethanesulphonamide*

A solution of the product of Stage (ii) (0.8g) in acetonitrile (40ml) containing N,N-dimethylmethyleneammonium chloride (0.6g) was stirred at room temperature for 3h. The resulting solution was partitioned between sodium carbonate (2N, 50ml) and ethyl acetate (2×50ml). The organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a solid. Trituration with ether gave the *title compound* as a solid (0.9g) m.p. 156-159°.

(iv) *3-(Cyanomethyl)-N,N-dimethyl-1H-indole-5-ethanesulphonamide*

Iodomethane (1.1ml) was added to a stirred solution of the product of Stage (iii) (2.7g) in dry dimethylsulphoxide (30ml) and the resulting solution stirred at room temperature for 10min. Potassium cyanide (2.7g) was added, and the resulting mixture stirred at room temperature overnight. The mixture was partitioned between sodium carbonate (2N, 300ml) and ethyl acetate (2×100ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was purified by 'flash' chromatography (J, 5cm col.) to give the *title compound* as a solid (1.3g) m.p. 105-107°.

(v) *3-(2-Aminoethyl)-N,N-dimethyl-1H-indole-5-ethanesulphonamide, compound with creatinine and sulphuric acid (1:1:1)*

A solution of the product of Stage (iv) (0.2g) in ethanol (40ml) containing concentrated hydrochloric acid (0.1ml) was hydrogenated at room temperature and pressure over 10% palladium oxide on charcoal (50% aq. paste, 0.2g) for 24h. The catalyst was filtered off, and the filtrate evaporated *in vacuo* to give an oil. The oil was partitioned between hydrochloric acid (2N, 20ml) and ethyl acetate (20ml). The aqueous layer was basified (Na_2CO_3) and extracted with ethyl acetate (2×20ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the tryptamine as an oil (0.05g) which was dissolved in a hot mixture of ethanol (9ml) and water (1ml), and a solution of creatinine in sulphuric acid (2M, 1:1 0.09ml) added. Filtration of the cooled mixture gave the title *compound* as a solid (0.05g) m.p. 223-225° (dec.).

Analysis Found: C,39.9;H,6.2;N,15.85;

$C_{14}H_{21}N_3O_2S.C_4H_7N_3O.H_2SO_4.2H_2O$ requires C,39.9;H,6.3;N,15.5%

N.m.r. δ(CD_3SOCD_3)2.82(6H,s,SO_2NMe_2),2.9-3.4(8H,m,$CH_2CH_2SO_2N$ and $CH_2CH_2NH_2$),7.0-7.55(4H,m,aromatic).

Example 9

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide, compound with creatinine, sulphuric acid and water (1:2:1.5:2)

A solution of the product of Preparation 5 (0.4g) in ethanolic dimethylamine (33% w/w, 25ml) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium oxide on charcoal (50% aq. paste, 0.7g) for 3h. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give an oil (0.35g), which was purified by flash chromatography (B, 8cm dia. col.). The resulting oil (0.25g) was dissolved in hot ethanol (20ml) and water (2.5ml) and treated with an aqueous solution of creatinine and sulphuric acid (1.1, 2M, 0.4ml) and cooled to 5° to deposit the *title compound* as a solid (0.22g), m.p. 193-197°.

Analysis Found: C,38.2;H,5.6;N,17.0.

$C_{15}H_{23}N_3O_2S.2C_4H_7N_3O.1.5H_2SO_4.2H_2O$ requires C,38.45;H,6.05;N,17.5%.

n.m.r characteristics agreed with those in Example 10.

Example 10

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride

Method (I)

A suspension of 10% palladium oxide on charcoal (14g, 50% paste with water) in ethanol (100ml) was prehydrogenated for 20min. To this was added the product of Preparation 5 (8g) in ethanolic dimethylamine (33% w/v, 400ml) and the resulting suspension stirred for 18h at 20° under an atmosphere of hydrogen. The suspension was filtered through hyflo and evaporated to give an oil (8.4g) which was purified by flash chromatography (8cm dia. col.) to give the tryptamine as an oil (6.0g). The oil was extracted with diethyl ether (2 1) and ethyl acetate (200ml) to leave a residue (0.5g) which was discarded. The organic extracts were combined, evaporated *in vacuo* and dissolved in analar ethyl acetate (300ml). Ethereal hydrogen chloride was added dropwise with rapid stirring. The resulting crystals were collected by filtration, washed with ether (100ml) and dried at 60° for 16h to give the *title compound* (5.5g) m.p. 137-139°

Analysis Found: C,51.8;H,6.7;N,11.9.

$C_{15}H_{23}N_3O_2S.HCl$ requires C,52.1;H,7.0;N,12.15.

N.m.r. (CD_3SOCD_3)2.65(3H,d,*Me*$NHSO_2$),2.84(6H,s,NMe_2),3.0-3.45(8H,m,$CH_2CH_2NMe_2$ and $NHSO_2CH_2CH_2$),7.0-7.6(5H,m,aromatic + $NHSO_2$).

Method (II)

(i) *5-[2-[(Methylamino)sulphonyl]ethyl]-1H-indole-3-acetic acid*

A solution of the product of Preparation 5 (0.3g) in ethanol (15ml) and water (15ml) containing potassium hydroxide (1.5g) was heated at reflux for 18h, cooled and the ethanol evaporated *in vacuo*. The residue was partitioned between hydrochloric acid (2N, 50ml) and ethyl acetate (2 × 50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by 'flash' chromatography (M, 3cm dia. col.) to give the *title compound* as an oil which crystallised on standing (0.1g) m.p. 123-125°C.

(ii) *3-(2-Hydroxyethyl)-N-methyl-1H-indole-5-ethanesulphonamide*

A solution of the product of Stage (i) (1.0g) in dry tetrahydrofuran (THF, 50ml) containing lithium aluminium hydride (1.0g) was heated at reflux, under nitrogen, for 6h. The resulting mixture was cooled, and excess reducing agent decomposed by adding excess 10%aq. THF. The resulting mixture was partitioned between sodium carbonate (2N, 50ml) and ethyl acetate (2 × 50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was purified by 'flash' chromatography (N, 4cm dia. col.) to give the *title compound* as an oil (0.35g)

T.l.c. (N) Rf 0.4 (Co^{IV})

(iii) *3-[2-(Dimethylamino]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride*

A solution of triphenylphosphine (0.44g) in tetrahydrofuran (THF, 3ml) was added, in one portion, to a solution of N-bromosuccinimide (NBS, 0.3g) in THF (5ml) giving a precipitate. A solution of the product of Stage (ii) (0.39g) in THF (10ml) was added, and the mixture stirred at room temp. for 18h. A solution of dimethylamine (33% w/v in ethanol, 20ml) was added, and the resulting solution stirred at room temp. for 3 days then evaporated *in vacuo* and the residue partitioned between hydrochloric acid (2N, 25ml) and ethyl acetate (2 × 25ml). The aqueous layer was basified (Na_2CO_3) and extracted with ethyl acetate (2 × 25ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was purified by 'flash' chromatography (A, 4cm dia. col.) to give pure free base as an oil (0.08g). This oil was dissolved in absolute ethanol (5ml) acidified with ethereal hydrogen chloride, and diluted with dry ether to precipitate the *title compound* as a hygroscopic solid which was shown by n.m.r. and t.l.c. (A, Rf 0.4) to be identical with the product of Method (I).

Method (III)

(i) *4-[2-[4-(Dimethylamino]butylidene]hydrazino]-N-methylbenzeneethanesulphonamide*

4,4-Dimethoxy-N,N-dimethylbutanamine (0.87g) was added to a solution of the product of Preparation 3 (2.0; purity *ca* 65%) in water (40ml), 2N hydrochloric acid (2.2ml) was added, and the mixture (pH~1.5) was stirred at room temp. under nitrogen for 4h. Further acetal (160mg) was added, and stirring was continued at room temp. for 1h. The mixture was basified with 8% aqueous sodium bicarbonate (20ml) and extracted with chloroform (3 × 70ml); the aqueous layer was saturated with sodium chloride and extracted again with chloroform (3× 120ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give an oil (2.25g). A sample (113mg) of the oil was purified by flash chromatography (U, 2cm dia. col.) to give the *title compound* as an oil (71mg)
T.l.c. (U) Rf 0.4 (IPA)

(ii) *3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride*

The product of Stage (i) (2.1g) was heated under reflux with polyphosphate ester (10.5g) in chloroform (40ml) with stirring under nitrogen for 8 min. The mixture was poured onto ice, stirred for 1.75h, basified with 2N sodium carbonate (100ml), and extracted with chloroform (3 × 250ml). The organic layers were dried ($MgSO_4$) and evaporated to give an oil (1.96g). Partial purification by flash chromatography (0,3cm dia. col) gave an oil (0.726g); further purification by short path chromatography gave the pure free base also as an oil (0.56g). The oil was warmed with analar ethyl acetate (30ml), and a portion (12ml) of the solution was filtered and acidified with ethereal hydrogen chloride (to pH2). The resulting precipitate was washed by decanting with dry ether and dried *in vacuo* (60°, 17h) to present the *title compound* as a hygroscopic solid (129mg) which was shown by n.m.r. and t.l.c. (0, Rf 0.25) to be identical with the product of Method (I).

Method (IV)

(i) *N,N-Dimethyl-5-[2-[(methylamino)sulphonyl]ethyl]-1H-indole-3-acetamide*

A mixture of N,N'-carbonyl-diimidazole (0.57g) and the product of Method (II) Stage (I) (0.9g) in freshly distilled tetrahydrofuran (25ml) was stirred at room temperature for 1h. The mixture was then cooled to 0°C and dimethylamine (2ml) added. After stirring (at 0°C) for 2h the solvent was removed under reduced pressure. The residue was chromatographed (P) to give *the title compound* as an oil (0.53g). T.l.c. (P) Rf 0.25 (Ce^{IV})

(ii) *3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride*

A solution of the product of Stage (I) (0.15g) in freshly distilled tetrahydrofuran (5ml) was added to a cold (0°) suspension of lithium aluminium hydride (87mg) in freshly distilled tetrahydrofuran (10ml) under nitrogen and the mixture heated at reflux for 2h. The cooled mixture was added to saturated potassium carbonate solution (15ml) and the organic phase separated. The aqueous phase was extracted with ethanol (20ml) and the combined organic phases evaporated under reduced pressure to give an oil which was dissolved in absolute alcohol (1ml) and ethreal hydrogen chloride solution (3ml) added. The solvent was removed by evaporation under reduced pressure and the residue triturated with ethyl acetate- cyclohexane (1:1) to give the *title compound* (0.1g) m.p. 132-134°, which was shown by t.l.c. (B, Rf 0.1) and n.m.r. to be identical with the product of Method (I).

Method (V)

(i) *(E)-2-(1H-indol-5-yl)-N-methylethenesulphonamide*

A mixture of 5-bromoindole (6.6g), N-methylethenesulphonamide (5.1g) palladium (II) acetate (75mg), tri-o-tolylphosphine (0.2g), triethylamine (12ml), and acetonitrile (5ml) was heated at 100° in an autoclave for 3h. The reaction mixture was cooled and partitioned between hydrochloric acid (1N, 300ml) and ethyl acetate (2×150ml). The combined extracts were dried, (Na_2SO_4) and evaporated *in vacuo* to give an oil which was purified by 'flash' chromatography (Q, 7cm dia. col.) to give the *title compound* as a solid (2.3g) m.p. 164-166°.
T.l.c. (Q) Rf 0.25 (Ce^{IV})

(ii) *N-Methyl-1H-indole-5-ethanesulphonamide*

A solution of the product of Stage (i) (2.3g) in a mixture of ethyl acetate (30ml) and methanol (15ml) was hydrogenated at room temperature and pressure over 10% palladium oxide on charcoal (50% aq. paste, 0.2g) for 4h until hydrogen uptake ceased (240ml). The catalyst was filtered off, and the filtrate evaporated *in vacuo* to give an oil which was crystallised from ethyl acetate to give the *title compound* as a solid (1.8g) m.p. 122-124°.
T.l.c. (R) Rf 0.4 (Ce^{IV}).

(iii) *N,N-Dimethyl-5-[2-[(methylamino)sulphonyl]ethyl]-α-oxo-1H-indole-3-acetamide*

Oxalyl chloride (0.3ml) was added dropwise, under nitrogen, to a stirred solution of the product of Stage (ii) (0.7g) in tetrahydrofuran (30ml) and the resulting solution stirred at room temperature for 1h. Dimethylamine gas was then bubbled through the solution for 10min. The resulting suspension was partitioned between hydrochloric acid (2N, 50ml) and ethyl acetate (2×50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was purified by 'flash' chromatography (S, 4 cm dia. col). The resulting oil was crystallised from a mixture of ethyl acetate and hexane to give the *title compound* as a solid (0.4g) m.p. 151-153°.

(iv) *3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride hemihydrate*

A solution of the product of Stage (iii) (0.3g) in tetrahydrofuran (30ml) containing lithium aluminium hydride (0.3g) was heated at reflux for 3h, cooled, and excess reducing agent decomposed by addition of 10% aq. THF. The resulting mixture was partitioned between sodium carbonate (2N, 100ml) and ethyl acetate (2×50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was purified by 'flash' chromatography (A, 4cm dia. col.). The resulting oil (0.15g) was dissolved in absolute ethanol (5ml), acidified with ethereal hydrogen chloride and the salt precipitated by adding excess dry ether. The salt was filtered off, and dried *in vacuo* to give the *title compound* as a solid (0.12g). m.p. 86-92° C (softens at 62°C) which was shown by n.m.r. and t.l.c. (A, Rf 0.4) to be identical with the product of Method (I).

Method (VI) A solution of the product of Example 1 as the free base (0.4g) in n-propanol (16ml), chilled in an ice-bath was treated with aqueous formaldehyde (~40% soln, 0.84ml) and the resultant suspension stirred for 0.75h, under an atmosphere of nitrogen. Sodium borohydride (0.54g) was added and the resulting mixture stirred in an ice-bath for 2h. The suspension was treated with 2N hydrochloric acid (~6ml), and stirred for 10min. The resulting mixture was evaporated to low volume (keeping the temperature below 50°) basified with 8% aq. sodium bicabornate solution (20ml) and extracted with ethyl acetate (5×15ml). The combined extracts were dried ($MgSO_4$) and evaporated to produce an oil (0.35g) which was chromatographed (B) to give the trytamine as an oil (0.148g). Part of the oil (0.140g) in absolute ethanol (2ml) was treated with excess ethereal HCl (4ml) and evaporated to dryness to leave a semi-solid which was triturated with anhydrous ether to present the *title compound* as a solid (0,1g) m.p. 130-136 (softens at 128°) which was shown by n.m.r and t.l.c. (A, Rf 0.3) to be identical with the product of Method (I).

Method (VII)

To a solution of the product of Example 12 (146mg) in anhydrous tetrahydrofuran (15ml) at ambient temperature was added tetrabutylammonium fluoride (0.99ml 1.0M solution in THF). After stirring at ambient temperature for a period of 40min, propylene oxide (100μl) was added followed by methyl iodide (1ml of 0.25M soln. in THF) and the mixture kept for 40min at ambient temperature, then quenched with aqueous sodium thiosulphate solution (20ml, 10% solution) and extracted with ethyl acetate (2×15ml). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. T.l.c. examination (D) of the reaction mixture indicated the presence of the *title compound* (Rf 0.50) which was identical with a sample prepared by Method (I).

Example 11

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide oxalate

A hot solution of the product of Example 10 as the free base (0.13g) was treated with oxalic acid (40mg) in ethanol (2ml) and the oxalate salt precipitated at once. Solvent was evaporated and the residual solid crystallised from hot methanol (10ml) to give the *title compound* as a solid (80mg) m.p. 198-199°.
Analysis Found: C,50.9;H,6.2;N,10.4.
$C_{15}H_{23}N_3O_7S.C_2H_2O_4$ requires C,51.1;H,6.3;N,10.5%.
T.l.c. (L) Rf 0.2 (IPA, Co).

Example 12

3-[2-(Dimethylamino)ethyl]-1H-indole-5-ethanesulphonamide oxalate

A mixture of the product of Example 18 stage (v) (70mg) in liquid ammonia (15mℓ) was heated in an autoclave at 110°C for 3h and then at 175°C for an additional 2h. On cooling to ambient temperature, ammonia was allowed to evaporate off and the autoclave recharged with pyridine (2ℓ) and liquid ammonia (15mℓ). After 14h at 155°C, the autoclave was cooled to ambient temperature and ammonia left to evaporate. The mixture was concentrated *in vacuo* and the resulting gum purified by flash chromatography to afford the product as a glass, (15.3mg) which was taken up in ethanol (0.25mℓ), filtered and added to a solution of oxalic acid (4.6mg) in ethanol (0.5mℓ). On concentrating *in vacuo*, a solid deposited, which was filtered, washed with ether and dried *in vacuo* overnight to afford the *title compound*, (5mg).

T.l.c. (A) Rf 0.23 (IPA,$KMnO_4$).

N.m.r. δ(CD_3SOCD_3)2.83(6H,s,NMe_2),3.0-3.4(8H,m,CH_2CH_2-NMe_2 and $CH_2CH_2SO_2$), 6.92(2H,br,SO_2NH_2), 7.0-7.6(4H,m,aromatic).

Example 13

3-[2-(Dimethylamino)ethyl]-1H-indole-5-ethanesulphonamide

(i) *(E)-2-[3-(Cyanomethyl)-1H-indol-5-yl]ethenesulphonamide*

A solution of ethenesulphonamide (428mg), 5-bromo-3-(cyanomethyl)-1*H*-indole (940mg), palladium II acetate (21mg) tri-o-tolylphosphine (67mg) and dry triethylamine (1.1mℓ) in dry acetonitrile (15mℓ) was heated in an autoclave at 130°C for 48h. On cooling to ambient temperature, the mixture was poured into water (30 mℓ) and extracted with ethyl acetate (3×30mℓ). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (B) of the residue afforded a powder. Recrystallization (hexane-dichloromethane) afforded the *title compound* as a powder (550mg) m.p. 176-178°.

(ii) *3-(Cyanomethyl)-1H-indole-5-ethanesulphonamide*

A solution of the product of stage (i) (443.6mg) in absolute ethanol (50mℓ) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium oxide on charcoal (1.30g, 50% aqueous paste in absolute ethanol, 30mℓ) for a period of 18h. The catalyst was removed by filtration through a sand-celite pad, which was then washed well with ethanol (200mℓ). The combined filtrates were concentrated *in vacuo* and the residue purified by flash (B) chromatography to afford a viscous oil, which solidified on trituration with diethyl ether to afford the *title compound* as an amorphous powder. (260mg) m.p. 109-110°.

(iii) *3-[2-(Dimethylamino)ethyl]-1H-indole-5-ethanesulphonamide*

A solution of the product of stage (ii) (4.9mg) in ethanolic dimethylamine (33%, 5mℓ) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium oxide on charcoal (10mg, 50% aqueous paste, pre-reduced in absolute ethanol, 5mℓ) for 14h. The mixture was filtered through a sand-celite pad, which was then washed with further quantities of ethanol (3×10mℓ), and the combined filtrates concentrated *in vacuo*. Flash chromatography (A) of the residue afforded the *title compound* (3.7mg) which was shown by t.l.c. (A. Rf 0.22) and n.m.r. to be identical with the product of Example *12*.

Example 14

3-[2-(Ethylmethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride

(i) *N-Ethylmethyl-5-[2-[(methylamino)sulphonyl]ethyl]-1H-indole-3-acetamide*

A solution of the product of Example 10 (II) stage (I) (0.7g) in dry tetrahydrofuran (THF) (50mℓ) containing carbonyldiimidazole (0.5g) was stirred at room temperature for 1h. N-Methylethylamine (2mℓ) was added, and the solution stirred at room temperature for 3h. The solution was partitioned between 2N hydrochloric acid (50mℓ) and ethyl acetate (2×50mℓ). The combined extracts were washed with 2N sodium carbonate (50mℓ), dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. The oil was purified by 'flash' chromatography eluting with ethyl acetate to give the *title compound* as an oil (0.2g).

T.l.c. ethyl acetate (Ce^{IV}) Rf 0.2.

(ii) *3-[2-(Ethylmethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide hydrochloride*

A solution of the product of stage (i) (0.2g) in dry THF (50mℓ) containing lithium aluminium hydride (0.2g) was heated at reflux for 24h, cooled, and excess reducing agent decomposed by addition of 10% aq. THF. The resulting mixture was partitioned between 2N sodium carbonate (50mℓ) and ethyl acetate (2×50mℓ). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil, which was dissolved in ethanol (5mℓ), acidified with ethereal hydrogen chloride and the salt precipitated by adding excess dry ether (300 mℓ). The salt was filtered off and dried *in vacuo* to give the *title compound* as a hygroscopic solid. (0.08g) m.p. 95°-99°C

Analysis Found: C,53.0;H,7.6;N,11.4.

$C_{16}H_{29}N_3O_2S.HCl$ requires C,53.4;H,7.3;N,11.7%.

N.m.r. δ(CD_3SOCD_3)1.28(3H,t,CH_2CH_3),2.65(3H,d,SO_2NHCH_3),2.81(3H,s,CH_2NCH_3),3.0-3.5(m,$CH_2CH_2SO_2$ and CH_2CH_2NMe and NCH_2CH_3),7.0-7.6(5H,m,aromatics + SO_2NH).

Example 15

N-Methyl-3-[2-(2-propenylamino)ethyl]-1H-indole-5-ethanesulphonamide oxalate

(i) *5-[2-[(Methylamino)sulphonyl]ethyl]-N-(2-propenyl)-1H-indole-3-acetamide*

A solution of the product of Example 10 (II) stage (i) (0.7g) in dry tetrahydrofuran (THF) (50mℓ) containing carbonyldiimidazole (0.5g) was stirred at room temperature for 1h. Allylamine (2mℓ) was added, and the solution stirred at room temperature for 3h. The solution was partitioned between 2N hydrochloric acid (50mℓ) and ethyl acetate (2×50mℓ). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. The oil was purified by 'flash' chromatography eluting with ethyl acetate to give the *title compound* as an oil (0.25g) which crystallised on standing. m.p. 123-125°C.

(ii) *N-Methyl-3[2-(2-propenylamino)ethyl]-1H-indole-5-ethanesulphonamide oxalate*

A solution of the product of stage (i) (0.2g) in dry THF (50mℓ) containing lithium aluminium hydride (0.4g) was heated at reflux for 24h, cooled, and excess reducing agent destroyed by adding 10% aq. THF. The resulting mixture was partitioned between 5N hydrochloric acid (50mℓ) and ethyl acetate (30mℓ). The aqueous layer was basified (Na_2CO_3) and extracted with ethyl acetate (2×50mℓ). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil (82mg), which was dissolved in ethanol (5mℓ), acidified with a solution of oxalic acid (25mg) in methanol (2mℓ) and the solution evaporated *in vacuo*. Trituration with dry ether gave the *title compound* as a solid. (80mg) m.p. 105-108°C.

Analysis Found: C,49.7;H,6.2;N,9.6.

$C_{16}H_{23}N_3O_2S.C_2H_2O_4.1.5H_2O$ requires C,49.3;H,6.4;N,9.6%.

N.m.r. (free base) δ(CD_3SOCD_3)2.65(3H,s,SO_2NHMe),3.0-3.4(10H,m,$CH_2CH_2SO_2$ and CH_2CH_2N and $NCH_2CH=$),5.17(2H,m,$-CH=CH_2$), 5.88(1H,m,$-CH=CH_2$), 7.0-7.5(4H, m,aromatic).

Example 16

N-Methyl-3-[2-[(phenylmethylidene)amino]ethyl]-1H-indole-5-ethanesulphonamide

A solution of the free base of the product from Example 1 (1.0g) in absolute ethanol (10mℓ) containing freshly distilled benzaldehyde (0.04g) and 3Å molecular sieves (0.5g) was stirred under nitrogen at reflux for 2h and then at room temperature for 48h. The suspension was filtered through "hyflo" and the filtrate evaporated under reduced pressure to produce a gum (0.036g). Trituration with anhydrous ether presented the *title compound* as a powder (0.01g) m.p. 146-148°.

N.m.r. δ(CD_3SOCD_3/$CDCl_3$)2.72(3H,d,SO_2NHMe)3.08-3.32(6H,m,$CH_2CH_2SO_2$ and $CH_2CH_2N=$), 6.3(1H,brq,SO_2NH)7.38-7.7(6H,m,$N=CH-Ph$ and Indole-4)8.18(1H,s,$N=CH$).

Example 17

3-[2-(Dimethylamino)ethyl]-N-(2-propenyl)-1H-Indol-5-ethane-sulphonamide

A solution of the product of Example 18 stage (v) (30mg) and allylamine (2mℓ) in dry pyridine was heated to 100° in a "reactivial" for 36h. The cooled reaction mixture was concentrated *in vacuo* and purified by 'flash' chromatography (A) to afford the *title compound* as a viscous oil (3.4mg).

T.l.c. (A) Rf 0.36 (IPA)

N.m.r. δ(CD_3SOCD_3)2.26(6H,s,NMe_2) 3.68(2H,brt, $CH_2CH=CH_2$)5.17(1H,dd,$CH=CH_2$,E-proton), 5.32(1H,dd,$CH=CH_2$, z-proton)5.9(1H,ddt,$CH=CH_2$), 7.4(2H,br,SO_2NH and Indole-4).

Example 18

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-Indole-5-ethanesulphonamide

(i)Phenyl 4-nitrobenzeethanesulphonate

To a solution of 4-nitrobenzeneethanesulphonyl chloride (14.4g) in benzene (200mℓ) and tetrahydrofuran (THF) (5mℓ) was added phenol (5.5.g) and triethylamine (8.5mℓ) on THF (20mℓ) with ice cooling and the resulting suspension was stirred at room temperature for 1h. The resulting mixture was washed with dilute hydrochloric acid (2×20mℓ), dried ($MgSO_4$) and concentrated to an oil, which solidified on standing. The solid was washed with ether (400mℓ) and air-dried for 1h to give the phenylsulphonate (11.45g). A sample (400mg) was recrystallised from ethanol (20mℓ) to give the *title compound* as a solid (250mg) m.p. 90-91°

(ii) *Phenyl 4-aminobenzeneethanesulphonate hydrochloride*

To pre-reduced 10% palladium oxide (2g; as 50% paste with water) in ethanol (50mℓ) was added a suspension of the product of stage (i) (11g) in ethanol (100mℓ) and ethyl acetate (200mℓ) which was hydrogenated at atmospheric pressure and temperature for 2h. Hydrogen uptake was 1.9ℓ. The catalyst was filtered off (Hyflo), washed with more ethanol (250mℓ), the solvent evaporated and the residual oil dissolved in chloroform (200mℓ). Ethanolic hydrogen chloride was added to the solution (to pH1) and the *title compound* precipitated as a solid (3.1g)

T.l.c. methylene chloride Rf 0.25 (Ce^{IV})

(iii) *Phenyl 4-hydrazinobenzeneethanesulphonate hydrochloride*

To a suspension of the product of stage (ii) (1g) in conc. hydrochloric acid (10mℓ) and water (10mℓ) was added sodium nitrite (0.46g) in water (2mℓ) at −5° (ice-salt bath). More water was added (20mℓ), the resulting suspension filtered and the filtrate added to a solution of stannous chloride (6.6g) in conc. hydrochloric acid (10mℓ) at −5°. The mixture was stirred at room temperature for 16h. The resulting solid was filtered off, washed with ether (50mℓ) and air-dried for 30 min, to give the *title compound* (0.51g) contaminated with inorganic material. This was used in the next step without further purification.
T.l.c. (A) Rf 0.75

(iv) *Phenyl 4-[2-[4-(dimethylamino)butylidene]hydrazino]benzene ethanesulphonate*

A suspension of the product of stage (iii) (0.5g) and 4,4-dimethoxy-N,N-dimethylbutanamine (0.5g) in water (10mℓ) and dilute hydrochloric acid (2N; 5mℓ; pH 1) was stirred at room temperature for 2h. The resulting solution was saturated with potassium carbonate and extracted with ethyl acetate (4×20mℓ). The extract was dried and evaporated to give the *title compound* as an oil (0.33g) which was used in the next step without further purification.
T.l.c. (A) Rf 0.5 (Ce^{IV}, IPA)

(v) *Phenyl 3-[2-(dimethylamino(ethyl]-1H-indole-5-ethanesulphonate*

The product of stage (iv) (0.33g) in polyphosphate ester (3.3g) and chloroform (8mℓ) was heated at reflux for 10 min, poured onto ice (20g) and neutralised with solid potassium carbonate. The aqueous layer was extracted with chloroform (4 × 15mℓ), the extracts combined, washed with brine (2×10mℓ), dried and evaporated. The residue was chromatographed (B) to give the slightly impure product as an oil (0.1g). A small sample (15mg) was re-purified by preparative layer chromatography (L, 20×20cm; 2mm) to give the pure *title compound* as an oil (7mg)
T.l.c. (A) Rf 0.5 (Ce^{IV}, IPA)

(vi) *3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-ethanesulphonamide*

The product of stage (v) (70mg) in a saturated solution of methylamine in pyridine (4mℓ) was heated at 100° in a "reactivial" for 1.5h. The mixture was concentrated and the residual oil purified by column chromatography (B) to give the *title compound* as an oil (7mg), which was shown by n.m.r. and t.l.c. (B, Rf 0.3) to be identical with the product of Example 10 method (i).

The following examples illustrate pharmaceutical formulations according to the invention, containing 3-[2-dimethylamino)ethyl]-N-methyl-1*H*-indole-5-ethanesulphonamide hydrochloride as the active ingredient. Other compounds of the invention may be formulated in a very similar manner.

Tablets for oral administration

These may be prepared by conventional methods such as direct compression or wet granulation;

A *Direct compression*

	mg/tablet	*For 20g Mix*
Active ingredient	2.24	0.448g
Calcium hydrogen phosphate B.P.*	95.26	19.052g
Croscarmellose sodium USP	2.00	0.400g
Magnesium stearate, B.P.	0.50	0.100g
Compression weight	100mg	

*of a grade suitable for direct compression

The active ingredient was sieved before use. The calcium hydrogen phosphate, croscarmellose sodium and active ingredient were weighed into a clean polythene bag. The powders were mixed by vigorous shaking for 5 minutes. The magnesium stearate was weighed, added to the mix which was blended for a further 2 minutes. The mix was then compressed using a Manesty F3 tablet machine fitted with 5.5mm flat bevelled edge punches, into tablets with target fill weight of 100mg.

B *Wet granulation*

	mg/tablet
Active ingredient	2.24
Lactose BP	151.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Capsules

	mg/capsule
Active Ingredient	26.00
*Starch 1500	174.00
Magnesium Stearate BP	1.00
Fill Weight	200.00

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No.2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

Syrup

		mg/5ml dose
Active Ingredient		26.00
Buffer	)	
Flavour	)	
Colour	)	
Preservative	)	
Thickening agent	)	
Sweetening agent	)	
Purified Water	to	5.00ml

The active ingredient, buffer, flavour, colour, preservative, thickening agent and sweetening agent are dissolved in some water, the solution is adjusted to volume and mixed. The syrup produced is clarified by filtration.

Suspension

		mg/5ml dose
Active Ingredient		26.00
Aluminium monostearate		75.00
Sweetening agent	)	
Flavour	)	as required
Colour	)	
Fractionated coconut oil	to	5.00ml

The aluminium monostearate is dispersed in about 90% of the fractionated coconut oil. The resulting suspension is heated to 115°C while stirring and then cooled. The sweetening agent, flavour and colour are added and the active ingredient is suitably dispersed. The suspension is made up to volume with the remaining fractionated coconut oil and mixed.

Tablet for buccal administration

	mg/tablet
Active ingredient	2.24
Lactose BP	94.56
Sucrose BP	86.7
Hydroxypropylmethylcellulose	15.0
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve and blended with the lactose, and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are then compressed into tablets using suitable punches.

Suppository for rectal administration

Active ingredient		5.6mg
* Witepsol H15	to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

Injection for intravenous administration

		mg/ml
Active ingredient		1.12mg
Sodium Chloride BP		as required
Water for Injection BP	to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

For Inhalation
Inhalation cartridges

		mg/cartridge
Active ingredient (micronised)		16.8
Lactose BP	to	25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The power blend is filled into No.3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

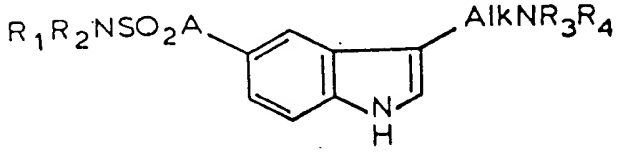
Metered dose pressurised aerosol

	mg/metered dose	*per can*
Active ingredient (micronised)	0.560	134.4mg
Oleic Acid BP	0.050	12mg
Trichlorofluoromethane BP	22.25	5.34g
Dichlorodifluoromethane BP	60.90	14.62g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into this solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering a metered dose of 85mg of suspension, are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

CLAIMS

1. A compound of the general formula (I) :



(I)

wherein

R_1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group;

R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl, phenyl, phen(C_{1-4})alkyl or C_{5-7} cycloalkyl group;

R_3 and R_4, which may be the same or different each represents a hydrogen atom or a C_{1-3} alkyl or 2-propenyl group or R_3 and R_4 together form an aralkylidene group;

Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups; and

A represents an alkylene chain containing two to five carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups,

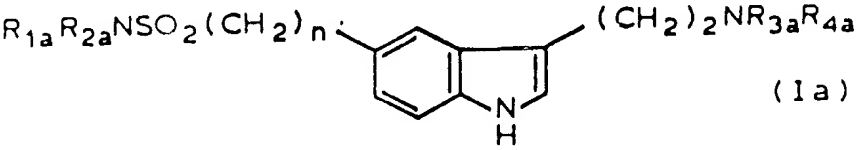
and the physiologically acceptable salts and solvates thereof.

2. A compound of general formula (I) or a physiologically acceptable salt or solvate thereof according to claim 1, wherein one or both of R_1 and R_2 represents a hydrogen atom.

3. A compound of general formula (I) or a physiologically acceptable salt or solvate according to claim 1 or [illegible] wherein A and Alk represent unsubstituted alkylene chains.

4. A compound of general formula (I) or a physiologically acceptable salt or solvate thereof according to claim 3, wherein Alk represents an unsubstituted alkylene chain containing two carbon atoms.

5. A compound of general formula (Ia) :



(Ia)

wherein

R_{1a} represents a hydrogen atom or a C_{1-3} alkyl group;

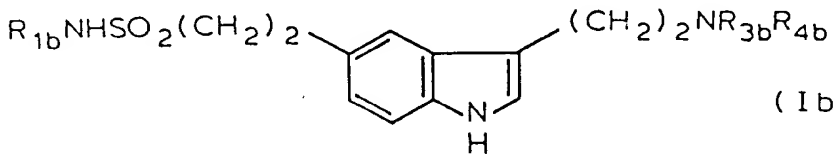
R_{2a} represents a hydrogen atom or a C_{1-3} alkyl, or phen (C_{1-3})alkyl group;

R_{3a} and R_{4a}, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group; and

n represents 2 or 3,

and physiologically acceptable salts and solvates thereof.

6. A compound of general formula (Ib):



(I b)

wherein

R_{1b} represents a hydrogen atom or a C_{1-3} alkyl group; and

R_{3b} and R_{4b}, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group;

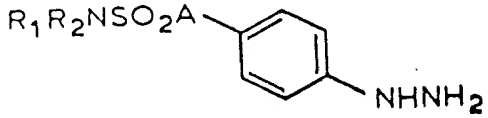
and physiologically acceptable salts and solvates thereof.

7. A physiologically acceptable salt of a compound according to any of claims 1 to 6 which is selected from the hydrochloride, hydrobromide, sulphate, fumarate, maleate and succinate.

8. A pharmaceutical composition which comprises at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof together with a physiologically acceptable carrier therefor.

9. A pharmaceutical composition according to claim 8 which is formulated for oral administration.

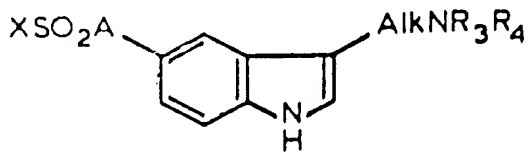
10. A compound of general formula (III) :



(III)

wherein R_1, R_2 and A are as defined for general formula (I) in claim 1 and salts thereof.

11. A compound of general formula (IX) :

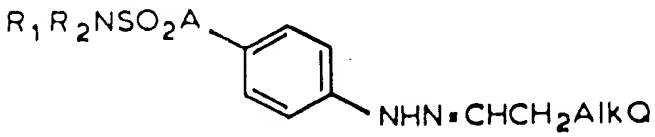


(IX)

wherein X represents a leaving group and A, Alk, R_3 and R_4 are as defined for general formula (I) in claim 1.

12. A process for the preparation of a compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof which process comprises

(A) cyclising a compound of general formula (II) :

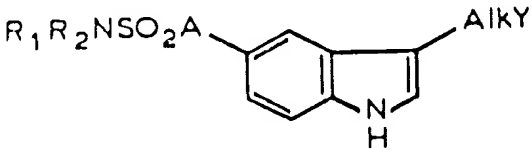


(II)

wherein

Q is the group NR_3R_4 or a protected derivative thereof or a leaving group and R_1, R_2, R_3, R_4, A and Alk are as defined for general formula (I); or

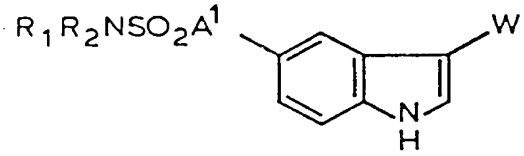
(B) reacting a compound of general formula (V) :



(V)

wherein Y is a readily displaceable group and R_1, R_2, A and Alk are as defined for general formula (I), or a protected derivative thereof, with a compound of formula R_3R_4NH where R_3 and R_4 are as defined for general formula (I); or

(C) reducing a compound of general formula (VI)



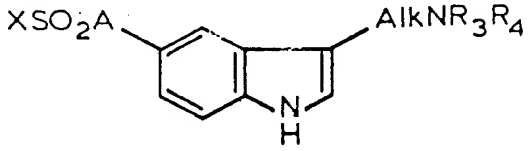
(VI)

wherein W is a group capable of being reduced to form the group $AlkNR_3R_4$ or to form a protected derivative of th $AlkNR_3R_4$ group

A^1 represents the group A or a group capable of being reduced to form the group A and R_1, R_2, R_3, R_4, Alk and A are as defined for general formula (I),

or a salt or protected derivative thereod; or

(D) reacting a compound of general formula (IX) :



(IX)

wherein X represents a leaving group and R_3, R_4, A and Alk are as defined for general formula (I) with an amine of general formula (X) :

(X)

wherein R_1 and R_2 are as defined for general formula (I); or

(E) converting a compound of general formula (I) or a salt or protected derivative thereof into another compound of general formula (I) or a salt or protected derivative thereof; or

(F) reacting a protected derivative of general formula (I) to remove one or more protecting groups; and if necessary and/or desired subjecting the compound thus obtained to one or more further reaction steps comprising

(G) (i) removing any protecting group or groups; and/or

(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

Printed in the UK for HMSO, D8818935, 8/85, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.